Usefulness of the Combination of In-Hospital Poor Diuretic Response and Systemic Congestion to Predict Future Cardiac Events in Patients With Acute Decompensated Heart Failure

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We aimed to (1) investigate the relation between diuretic response (DR) with or without systemic congestion and prognosis and (2) explore the potential predictors of poor DR for risk stratification in patients with acute decompensated heart failure (ADHF). We enrolled 186 consecutive patients hospitalized for ADHF. The DR was defined as (body weight at discharge − body weight at admission)/40 mg furosemide or equivalent loop diuretic dose. Systemic congestion on admission was simply evaluated by the presence of leg edema or jugular venous distention. All patients were divided into 4 groups based on the median of DR (−0.50 kg/40 mg) and the status of systemic congestion; GR/C (good DR with systemic congestion, n = 66), GR/N (good DR without systemic congestion, n = 27), PR/C (poor DR with systemic congestion, n = 48); and PR/N (poor DR without systemic congestion, n = 45). The composite outcome was defined as cardiac death and rehospitalization for worsening heart failure. In survival analysis, the cardiac event-free rate in PR/C was significantly lower than that in any other groups (log-rank, p <0.001), and PR/C was an independent predictor of cardiac events (hazard ratio 2.17, p = 0.016). In conclusion, the combination of in-hospital poor DR, characterized by previous ischemic heart disease, and prehospital dose of daily loop diuretics, and systemic congestion provides a risk stratification for future cardiac events in patients with ADHF.   © 2017 Elsevier Inc. All rights reserved. (Am J Cardiol 2017;119:2010−2016)

Acute decompensated heart failure (ADHF) is a leading cause of hospitalization with high social burden.[1−3] Exacerbating congestion is an essential target for ADHF because the residual congestion is considered to be associated with poor outcome,[4−6] and loop diuretics is a key agent of the treatment of HF.[1,7] Diuretic response (DR) is considered to be an important cornerstone of the successful treatment and poor prognosis of ADHF.[8−11] The early prediction of poor DR during hospitalization is important for the subsequent risk stratification and might lead to the optimal treatment strategies for ADHF.[8,12] However, although the treatment strategies for each patient with or without systemic congestion might differ,[1,13] the significance of DR is sometimes discussed as if it were the same between these 2 types of patients. The aim of this study was to (1) investigate the prognostic value of DR for patients with or without systemic congestion and (2) explore potential predictors of poor DR for risk stratification on admission in patients with ADHF.

Methods

We enrolled 186 patients with ADHF hospitalized at the Handa City Hospital in Japan from January 2013 to December 2013. On admission, HF was diagnosed by 2 expert cardiologists based on the Framingham criteria.[14] We assessed a set of physical findings that reflected cardiopulmonary and systemic congestion. Body weight (BW) was measured on admission and at discharge. Data on the total usage of loop diuretics during the hospitalization were collected from each electrical medical record for evaluating DR. Laboratory measurements were performed on admission, and echocardiography was performed under the individual stable condition of HF during the hospitalization. Estimated glomerular filtration rate was calculated using an equation modified for Japanese.[15] This observational study protocol complied with the Declaration of Helsinki and was approved by the Ethics Review Board of Handa City Hospital.

It is generally accepted that using BW change per unit of furosemide might provide an applicable metric to assess the DR or resistance.[10] In this study, we defined DR as an in-hospital change in BW (kg)/40 mg furosemide or equivalent loop diuretic dose and calculated DR according to the
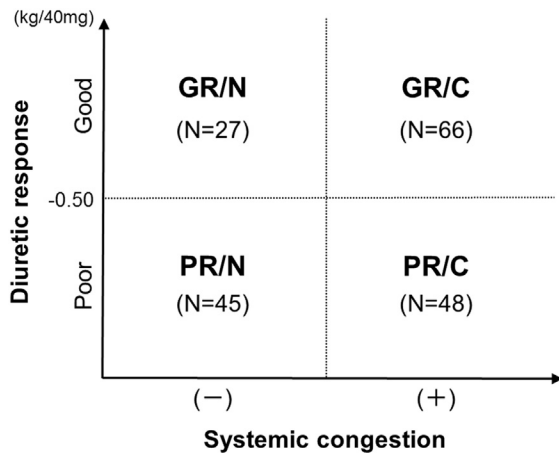
Figure 1. Definition of 4 groups.

formula, DR = (BW [discharge] − BW [admission]) × 40/the total usage of furosemide or equivalent dose. We converted loop diuretic dose to furosemide equivalents with 40 mg of intravenous furosemide, 80 mg oral furosemide, 20 mg oral torasemide, and 120 mg oral azosemide.[16,17] Systemic congestion on admission was simply defined as peripheral edema or jugular venous distention.

All patients were divided into 4 groups based on the median of DR and systemic congestion; GR/C (good DR [DR ≤ median; −0.50 kg/40 mg] with systemic congestion, n = 66), GR/N (good DR without systemic congestion, n = 27), PR/C (poor DR [DR > median] with systemic congestion, n = 48), and PR/N (poor DR without systemic congestion, n = 45; Figure 1). All patients were treated with optimal medical therapy and according to the current guidelines for HF[1,18] and were followed up for 1 year in attempting to uptitrate by expert cardiologists.[19] Composite end point was defined as cardiac death and rehospitalization for worsening HF. Unexplained sudden death was included in cardiac deaths.

Continuous variables are expressed as mean ± SD or as median and interquartile range for nonparametric variables. Categorical variables are described as numbers (percentages). Multiple comparisons between 4 groups were made by analysis of variance or Kruskal-Wallis test as appropriate. Kaplan-Meier survival curves plotted for cardiac events were compared by the log-rank test and followed Bonferroni's analysis. We used Cox proportional hazard regression models to determine the unadjusted and adjusted hazard ratios (HRs) for cardiac events and multiple logistic regression analyses for determinants of PR/C and poor DR. All potential confounders were entered in univariate analysis, and covariates with p <0.10 were retested for multivariate analysis. A p <0.05 was considered significant. All statistical analyses were performed using SPSS, version 18 (SPSS Inc., Chicago, Illinois).

Results

Baseline characteristics of all groups are listed in Table 1. There were significant differences in the duration of hospitalization, in-hospital BW change, and the dose of daily loop diuretics. However, the BW change and in-hospital dose of daily loop diuretics tended to be higher in PR/C and PR/N than GR/C and GR/N. PR/C had higher morbidity rate of ischemic heart disease, lower hemoglobin level, and higher blood urea nitrogen level.

Table 2 lists the medication profile during hospitalization and at discharge. Group PR/C needed the largest dose of daily loop diuretics not only during in-hospital but also before admission (Table 1) and at discharge. In contrast, the usage rates of renin-angiotensin system inhibitors, β blockers, and aldosterone antagonists were comparable at discharge.

During follow-up period, there were 63 rehospitalizations and 20 cardiac deaths, including 3 arrhythmic deaths. All arrhythmic deaths were occurred in PR/C group. In Kaplan-Meier survival analysis for cardiac events, PR/C had the lowest event-free survival rate compared with the other 3 groups (log-rank, p <0.001; Figure 2). In addition, PR/C had greater cardiac events than GR/C, GR/N, and PR/N (p <0.001, p = 0.021, and p = 0.005, respectively). The Cox proportional hazard analysis for cardiac event was listed in Table 3. PR/C and the hemoglobin level on admission were independent determinants of poor outcome (PR/C, HR 2.17, 95% CI 1.16 to 4.06, p = 0.016; hemoglobin, HR 0.87, 95% CI 0.77 to 0.98, p = 0.020).

We show the results of multivariate analysis for PR using patient characteristics on admission in Table 4. The history of ischemic heart disease (odds ratio 2.19; 95% CI 1.07 to 4.49; p = 0.032) and prehospital dose of daily loop diuretics (odds ratio 1.04; 95% CI 1.02 to 1.06; p <0.001) were independent determinants of PR. Receiver-operating characteristic analysis showed that a prehospital dose of 18 mg of oral furosemide or equivalent loop diuretic dose had a sensitivity of 0.710 and a specificity of 0.731 and a prehospital dose of 38 mg had a sensitivity of 0.892 and a specificity of 0.484 for the determinant of PR on admission.

Discussion

The main findings of the present study include the following: (1) the cardiac event-free rate was significantly lower only in PR/C and (2) the history of ischemic heart disease and the dose of daily loop diuretics on admission were significant determinants of poor DR. To the best of our knowledge, this is the first report to show the significance of the combined assessment with DR and systemic congestion for predicting cardiac events in patients with ADHF.

Previous studies demonstrated that the required increasing doses of loop diuretics and poor DR were associated with more advanced HF[20,21] because the diuretic dose-response curve pathophysiologically shifts downward and to the right in patients with HF.[22] More importantly, it has been suggested that poor DR strongly predicts mortality and HF rehospitalization.[8,9,23,24] However, BW change or urine volume would be largely dependent on the status of congestion. Actually, we presented the prognostic difference between PR/C and PR/N (Bonferroni, p = 0.005). Interestingly, the present data indicated that the DR in the PR/C

Table 1
Baseline characteristics

Variable	Overall (n=186)	GR/C (n=66)	GR/N (n=27)	PR/C (n=48)	PR/N (n=45)	P-value
Age (years)	78.1 ± 12.0	78.2 ± 11.1	76.3 ± 13.9	80.3 ± 8.6	76.7 ± 14.5	0.407
Men	82 (44%)	32 (48%)	11 (41%)	16 (33%)	23 (51%)	0.289
Body weight on admission (kg)	52.8 ± 13.1	56.2 ± 14.4*	54.7 ± 14.2	48.8 ± 11.1[†]	50.8 ± 13.1	0.012
Body weight at discharge (kg)	48.4 ± 11.7	49.7 ± 12.8	50.2 ± 13.4	45.5 ± 10.1	48.5 ± 10.4	0.227
NYHA class III or IV	131 (70%)	46 (70%)	16 (59%)	35 (73%)	34 (76%)	0.089
Systolic BP (mmHg)	151 ± 35	151 ± 29	154 ± 38	150 ± 39	151 ± 35	0.304
Diastolic BP (mmHg)	86 ± 23	88 ± 24	92 ± 26	80 ± 24	85 ± 18	0.084
Heart rate (beats/minute)	97 ± 27	96 ± 27	104 ± 27	95 ± 28	95 ± 27	0.950
Rales	127 (68%)	51 (77%)	15 (56%)	34 (71%)	27 (60%)	0.110
Jugular venous distention	70 (38%)	41 (62%)[‡, §]	0 (0%)[†, *]	29 (60%)[‡,§]	0 (0%)[†, *]	<0.001
Peripheral edema	114 (61%)	66 (100%)[‡, §]	0 (0%)[†, *]	48 (100%)[‡, §]	0 (0%)[†, *]	<0.001
LVEF (%)	44.1 ± 15.5	45.2 ± 13.7	40.6 ± 17.2	48.1 ± 15.7	40.2 ± 15.8	0.049
Duration of hospitalization (day)	17.7 ± 11.1	15.9 ± 8.0*	13.3 ± 4.0*	22.0 ± 13.7[†, ‡]	18.5 ± 13.2	0.003
Body weight change (kg)	−3.7 (−1.8 to −5.9)	−5.5 (−3.9 to −8.3)[*, §]	−3.6 (−2.6 to −5.8)[†, §]	−2.2 (−0.8 to −4.9)[†]	−1.9 (−0.8 to −3.5)[†, ‡]	<0.001
In-hospital dose of daily loop diuretics (mg/day)	38 (23−60)	30 (19−40)[*, §]	22 (18−37)[*, §]	58 (27−106)[†, ‡]	46 (37−77)[†, ‡]	<0.001
Diuretic response (kg/80mg)	−0.50 (−0.16 to −0.95)	−0.98 (−0.63 to −1.84)[*, §]	−0.88 (−0.69 to −1.42)[*, §]	−0.14 (−0.06 to −0.27)[†, ‡]	−0.18 (−0.04 to −0.33)[†, ‡]	<0.001
Medical history						
Hypertension	140 (75%)	51 (77%)	19 (70%)	37 (77%)	33 (73%)	0.884
Diabetes mellitus	65 (35%)	26 (39%)	4 (15%)	19 (40%)	16 (36%)	0.120
Ischemic heart disease	72 (39%)	20 (30%)*	7 (26%)*	27 (56%)	18 (40%)[†, ‡]	0.017
Valvular heart disease	85 (46%)	34 (52%)[‡]	4 (15%)[†, *, §]	24 (50%)[‡]	23 (51%)[‡]	0.006
Atrial fibrillation	75 (40%)	30 (45%)	8 (30%)	17 (35%)	20 (44%)	0.428
Current smoker	20 (11%)	4 (6%)	4 (15%)	3 (6%)	9 (20%)	0.076
Prior HF hospitalization	89 (48%)	25 (38%)*	4 (15%)[*, §]	35 (73%)[†, ‡]	25 (56%)[‡]	<0.001
Medication prior to admission						
ACE-Is/ARBs	87 (47%)	26 (39%)	8 (30%)*	30 (63%)[‡]	23 (51%)	0.020
Beta blockers	75 (40%)	23 (35%)	5 (19%)*	27 (56%)[‡]	20 (44%)	0.009
Aldosterone antagonists	44 (24%)	19 (29%)	2 (7%)	10 (21%)	13 (29%)	0.123
Thiazides	8 (4%)	3 (5%)	1 (4%)	4 (8%)	0 (0%)	0.270
Oral loop diuretics	106 (57%)	29 (44%)*	5 (19%)[*, §]	43 (90%)[†, ‡, §]	29 (64%)[‡, *]	<0.001
Dose of daily loop diuretics (mg/day)	20 (0−40)	0 (0−40)*	0 (0−0)[*§]	40 (20−75)[†, ‡, §]	20 (0−40)[‡, *]	<0.001
Chest X-ray on admission						
Pleural effusion	110 (59%)	42 (64%)	15 (56%)	32 (67%)	21 (47%)	0.196
Interstitial edema	168 (90%)	61 (92%)	24 (89%)	39 (81%)	44 (98%)	0.050
Laboratory data on admission						
Hemoglobin (g/dL)	11.5 ± 2.4	11.5 ± 2.2	12.2 ± 2.9*	10.5 ± 2.3[‡, §]	12.3 ± 2.3*	0.001
Blood urea nitrogen (mg/dL)	29.6 ± 21.1	23.7 ± 14.4*	28.8 ± 27.4	38.3 ± 24.5[†]	29.7 ± 18.4	0.003
Creatinine (mg/dL)	1.04 (0.74−1.52)	0.91 (0.70−1.16)*	0.91 (0.59−1.33)	1.33 (0.87−1.74)[†]	1.24 (0.84−1.74)	0.003
Estimated GFR (mL/min/1.73m^2)	48.6 ± 25.1	54.7 ± 21.5*	55.9 ± 27.3*	38.7 ± 20.8[†, ‡]	45.9 ± 29.2	0.002

					p Value
Sodium (mEq/L)	140 ± 5	141 ± 4	140 ± 6	140 ± 5	140 ± 4	0.349
Albumin (g/dL)	3.3 ± 0.5	3.2 ± 0.5	3.4 ± 0.4	3.3 ± 0.4	3.4 ± 0.6	0.142
Glucose (mg/dL)	162 ± 74	157 ± 73	153 ± 62	166 ± 86	168 ± 70	0.770
BNP (pg/mL)	728 (446−1233)	680 (387−1027)	651 (504−1437)	758 (440−1536)	753 (503−1558)	0.313

ACE-I = angiotensin converting enzyme inhibitor; ARB = angiotensin II receptor blocker; BP = blood pressure; BNP = brain natriuretic peptide; GFR = glomerular filtration rate; HF = heart failure; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

* Versus PR/C p <0.05.
† Versus GR/C p <0.05.
‡ Versus GR/N p <0.05.
§ Versus PR/N p <0.05.

had already been impaired before hospitalization, although we calculated DR as the in-hospital efficacy of loop diuretics. Group PR/C was exposed to the median of 40 mg/day loop diuretics on admission, and the dose of daily loop diuretics in PR/C was the highest among all groups (p <0.001, Table 1). In addition, 94% of PR/C was treated with loop diuretics. Nonetheless, they had systemic congestion on admission. This fact suggests that the DR in PR/C was impaired before the hospitalization. Group PR/N had a better prognosis compared with PR/C. The BW change during the hospitalization was the smallest in PR/N, potentially indicating that the main cause of ADHF in PR/N was not volume retention but central volume shift. Actually, 64% of PR/N patients required loop diuretics for the management of volume status before hospitalization (Table 1), and loop diuretics might effectively remove the excessive fluid volume in PR/N before hospitalization. We speculate that the diuretic resistance has yet to be formed in PR/N, which leads to a better outcome. Interestingly, all arrhythmic deaths were occurred in PR/C patients. It was suggested that PR/C was more advanced stage of HF than the other groups.[25] Conceivably, inadequate exposure to an overdose of loop diuretics might cause PR/N patients to progress to PR/C. Greater attention should be paid to the direction of loop diuretics in outpatients without systemic congestion, which might lead to an improved outcome by preventing the advance of diuretic resistance.

We revealed 2 determinants of PR groups on admission: history of ischemic heart disease and prehospital dose of loop diuretics (Table 4). Furthermore, receiver-operating characteristic analysis detected 2 cut-off points of pre-hospital oral dose of loop diuretics to predict PR as 18 or 38 mg/day. We might be able to stratify patients with ADHF into PR/C or PR/N according to these potential predictors and the presence or absence of systemic congestion. In PR/C, the favorable effect of loop diuretics can no longer be expected, unless there is an excessive volume. When patients with ADHF on admission had already been exposed to more than 20 to 40 mg of oral furosemide and had a history of ischemic heart disease, we should simply and quickly evaluate the status of congestion. In case of systemic congestion, we should then avoid administering more than the necessary loop diuretic dose needed[26] and choose an alternative diuretic strategy for ADHF treated with not only loop diuretics but also aqua-retics, thiazide, or any other diuretic agent. In addition, multivariate analysis for PR/C revealed that hemoglobin level was one of the independent determinants. The aggressive correction of anemia might be a promising treatment strategy for outpatient predicted PR/C.[27]

Several study limitations need to be addressed. First, this study was retrospective and consists of a relatively small number of Asian patients from a single center. As for the generalizability of our findings, further investigations for other populations were needed. Second, we assessed in a simple manner the systemic congestion by the presence of peripheral edema or jugular venous distention that was not quantitative. However, this swift and simple assessment might be fairly available for physicians and provide practical information about prognosis in a hectic acute setting.[28] Third, although using BW change per unit of furosemide is

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Table 2
Medication during hospitalization and at discharge

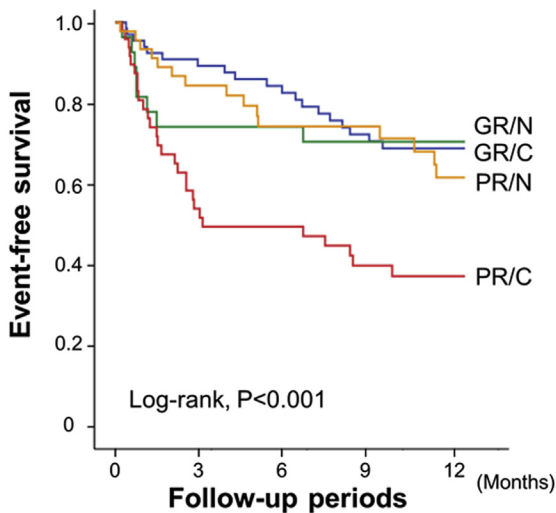| Variable	Overall (n=186)	GR/C (n=66)	GR/N (n=27)	PR/C (n=48)	PR/N (n=45)	P-value
Medication in hospital						
Dobutamine	15 (8%)	1 (2%)*	2 (7%)	8 (17%)†	4 (9%)	0.033
Milrinone	11 (6%)	1 (2%)*	1 (4%)	7 (15%)†	2 (4%)	0.026
Nitrates	41 (22%)	10 (15%)	7 (26%)	9 (19%)	15 (33%)	0.128
Medication at discharge						
Dose of daily loop diuretics (mg/day)	38 (20−44)	20 (16−40)*‡	20 (20−20)*‡	60 (25−80)†§	40 (40−60)†§	<0.001
ACE-Is/ARBs	137 (74%)	48 (73%)	18 (67%)	36 (75%)	35 (78%)	0.770
Beta blockers	140 (75%)	51 (77%)	20 (74%)	36 (75%)	33 (73%)	0.969
Aldosterone antagonists	86 (46%)	34 (52%)	13 (48%)	17 (35%)	22 (49%)	0.371

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

* Versus PR/C p <0.05.
† Versus GR/C p <0.05.
‡ Versus PR/N p <0.05.
§ Versus GR/N p <0.05.

Figure 2. Kaplan-Meier analysis for cardiac event. p <0.001 for log-rank test comparing all groups. PR/C had higher cardiac events than GR/C, GR/N, and PR/N (Bonferroni, p <0.001, p = 0.021, and p = 0.005, respectively).

GR/C	N at risk	66	55	48	41	36
	N of cardiac events	-	7	11	18	19
GR/N	N at risk	27	20	20	19	18
	N of cardiac events	-	7	7	8	8
PR/C	N at risk	48	23	21	15	13
	N of cardiac events	-	22	23	27	28
PR/N	N at risk	45	34	29	25	18
	N of cardiac events	-	7	11	11	15

Table 3
Cox proportional hazard analysis for cardiac event

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P-value	HR (95% CI)	P-value
PR/C*	2.90 (1.61−5.20)	<0.001	2.17 (1.16−4.06)	0.016
Age	1.03 (1.00−1.05)	0.035	1.01 (0.99−1.04)	0.306
Men	0.704 (0.43−1.14)	0.156	0.99 (0.57−1.69)	0.957
Hypertension	0.74 (0.44−1.23)	0.248		
Diabetes mellitus	1.22 (0.76−1.98)	0.414		
Hemoglobin	0.79 (0.72−0.87)	<0.001	0.87 (0.77−0.98)	0.020
Creatinine	1.08 (0.99−1.18)	0.103		
Blood urea nitrogen	1.02 (1.01−1.02)	<0.001	1.01 (1.00−1.02)	0.060
LogBNP	1.28 (0.67−2.42)	0.455		
LVEF	1.00 (0.98−1.01)	0.744		
Albumin	1.05 (0.66−1.68)	0.838		
Ischemic heart disease	1.26 (0.78−2.02)	0.349		
Valvular heart disease	1.36 (0.85−2.17)	0.203		
Duration of hospitalization	1.00 (0.98−1.03)	0.795		

Covariates with p <0.10 in univariate analysis and gender were entered in multivariate analysis.

BNP = brain natriuretic peptide; CI = confidence interval; HR = hazard ratio; LVEF = left ventricular ejection fraction.

* Compared with the other groups.

considered to provide an applicable metric to confirm the response to diuretics,[10] the standard definition of DR has not been scientifically established.[29] Although DR might be influenced by water or sodium intake, we could not collect these data in this study.

Disclosures

Table 4
Predictors of PR groups on admission

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	0.99 (0.97−1.02)	0.591		
Men	0.84 (0.47−1.50)	0.555		
Hypertension	1.00 (1.00−1.00)	0.514		
Diabetes mellitus	0.79 (0.43−1.44)	0.442		
Valvular heart disease	0.68 (0.38−1.21)	0.186		
Ischemic heart disease	2.29 (1.25−4.20)	0.007	2.19 (1.07−4.49)	0.032
Prior HF hospitalization	4.01 (2.18−7.39)	<0.001	1.75 (0.85−3.58)	0.128
Dose of daily loop diuretics	1.05 (1.03−1.06)	<0.001	1.04 (1.02−1.06)	<0.001
Blood urea nitrogen	1.02 (1.01−1.04)	0.006	1.00 (0.98−1.03)	0.785
Albumin	0.73 (0.41−1.31)	0.291		
Creatinine	1.64 (1.13−2.37)	0.008	0.98 (0.52−1.83)	0.939
LogBNP	1.29 (0.54−3.11)	0.569		
LVEF	1.00 (0.98−1.02)	0.831		

Covariates on admission with p <0.10 in univariate analysis and gender were entered in multivariate analysis.

BNP = brain natriuretic peptide; CI = confidence interval; HF = heart failure; HR = hazard ratio; LVEF = left ventricular ejection fraction.

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